台灣幹細胞應用協會
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NEWSLETTER
台內團字第1080060926號 促進幹細胞於人類健康與美麗上之福祉 總編輯 王振祥 博士

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癌細胞外泌體雙向玩弄免疫系統來助長癌症

王振祥 博士編撰

- 幹細胞外泌體不能胡亂使用，如用到癌症幹細胞或是發炎性的幹細胞衍生的外泌體，其對身體可能帶來疾病和癌症的風險。
- 癌細胞的外泌體會同時促進和壓抑人體的免疫系統，只是在該促進時壓抑，該壓抑時促進，以利癌細胞的入侵，轉移和擴增。
- 癌症的病患身體中已經流串著其外泌體的各種訊號因子，其免疫細胞已經受到這些因子影響而無法毒殺癌細胞。任何療法如果沒有徹底處理這些致癌訊號，一切都會是枉然，包括化放療，標靶藥物，基轉和非基轉免疫細胞療法等。
- 本人正在研發一種免疫細胞致癌訊號清洗，健康訊號重灌之免疫細胞修復技術，以恢復其對抗癌細胞的免疫力。
- 本文的專業度較深，非此領域的人士只要能掌握摘要重點即可。專業腫瘤科醫師幹則可以此論點為開端，進行其真理的探索。

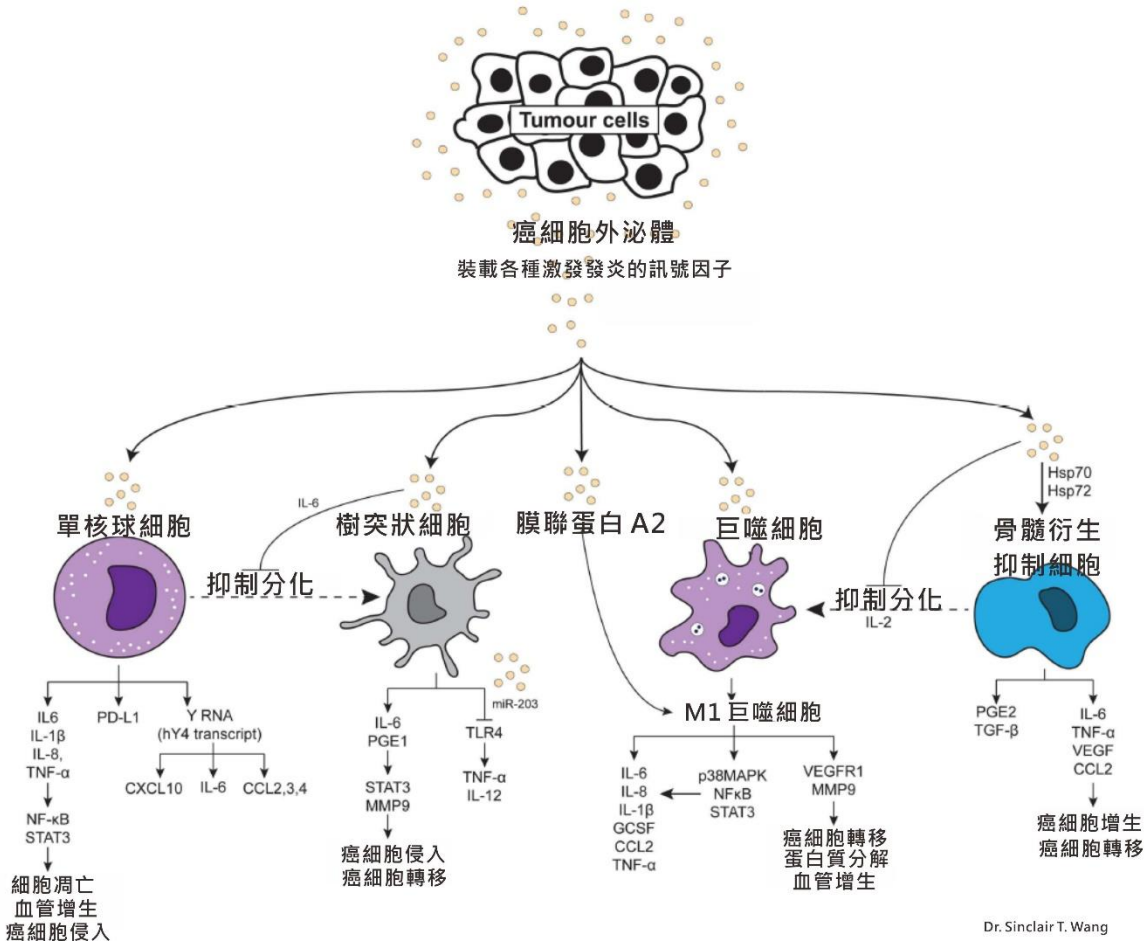
前言

外泌體在細胞間的通訊中起著不可或缺的作用，並通過傳遞信號和轉移其內容而起穿梭的作用，從而在疾病的生理和病理過程的調節中起著作用（1-3）。外泌體的載物由蛋白質，脂質，DNA（mtDNA，ssDNA，dsDNA）和 RNA（mRNA，miRNA，長非編碼 RNA）組成，它們

在轉移到受體細胞中時都具有某些功能（2-5）。來自腫瘤的外泌體通過其致癌成分的轉移而顯著地參與了其受體細胞的癌化。前列腺癌細胞衍生的外泌體通過運送致癌因子（例如 H-ras 和 K-ras 轉錄本）以及致癌的 miRNA miR- 125b，miR-130b 和 miR-155（6）。乳腺癌患者細胞和血清的外泌體能夠以切酶依賴的方式促進健康上皮細胞形成腫瘤（7）。結腸癌的外泌體從結腸腫瘤細胞的轉移能夠在體內和體外誘導受體細胞中細胞的增殖和化學抗性的升高（8）。新血管生成的上調也受到腫瘤來源的外泌體的影響。血癌細胞衍生的外泌體能夠將 miRNA（miR-92a）轉運至內皮細胞，從而調節內皮的遷移和淋巴管的形成（11）。黑色素瘤細胞中分離出的外泌體能夠刺激癌細胞轉移性小環境的形成（10）。由於外泌體包含了其來源的細胞的所有生物活性分子，因此有可能成為癌症診斷的生物標誌（11-15）。

外泌體具有促進或抑制免疫反應的能力。源自凝血酶活化的血小板的外泌體能夠刺激造血細胞的增殖，存活和趨化性（16），並激活單核細胞釋放促炎性細胞因子並誘導 B 細胞的活化（17）。由抗原呈遞細胞，例如淋巴細胞和樹突狀細胞釋放的外泌體包含 MHC I 類分子，它們能夠潛在地介導抗原特異性 T 細胞交叉啟動（18-22）。自然殺手（NK）細胞衍生的外泌體可通過其細胞內的穿孔素和顆粒酶 B 介導抗腫瘤活性，而顆粒酶 B 對多種腫瘤細胞系具有細胞毒活性（23）。肥大細胞衍生的外泌體中表達的肽可被提呈給樹突狀細胞以刺激特異性免疫反應（24）。外泌體的各種免疫抑制作用包括通過表達死亡配體 FasL（25）和 TRAIL（26），能促進活化 T 細胞的凋亡；單核細胞對樹突狀細胞分化的損害（27）；以及抑制 NK 細胞介導的細胞毒性反應（28）。

腫瘤外泌體的促發炎作用



腫瘤外泌體對免疫分子促發炎作用的後果

腫瘤外泌體對單核細胞的促發炎作用

在慢性炎症期間，細胞因子可促進在腫瘤微環境中創造理想的生長條件，並促進腫瘤生長的進程（29-31）。 腫瘤細胞及其相關的微環境可以產生改變單核細胞的募集，遷移，分化和

功能特性的分子（32）。腫瘤細胞產生和釋放的外泌體包可以傳遞給包括單核細胞在內的受體細胞以調節其行為。在 2013 年 Bretz 等人表明，從卵巢癌患者的惡性腹水獲得的外泌體能夠調節單核細胞的生物學功能（33），誘導多種促炎細胞因子的產生和分泌，包括 IL-6，IL-1b 和 IL-8，以及使 TNF-α（TNF）-a 活化，隨後激活 NFkB 以及 STAT3（33）。NFkB 的組成型激活與侵襲性表型有關，包括組織入侵和轉移以及對生長抑制的抵抗力（34）。NFkB 和 STAT3 一起具有調節細胞凋亡，血管生成和腫瘤侵襲的能力，因此能夠抵抗免疫監視（35）。另一研究發現 CLL 衍生的外泌體在單核細胞和巨噬細胞向腫瘤形成前表型的偏斜中起作用，並釋放腫瘤支持性細胞因子以及免疫抑制分子的表達，例如 PD-L1 來促進通過 TLR7 信號顯著增加 CCL2，CCL3，CCL4，CXCL10 和 IL-6 的分泌（36）。

腫瘤外泌體對巨噬細胞的促發炎作用

癌細胞和腫瘤相關巨噬細胞之間通過細胞外體進行細胞間通訊，可以調節這些免疫細胞的功能和表型。乳癌（37）和胃癌（38）來源的外泌體可通過激活 NFkB 在巨噬細胞中誘導 M1 促炎反應，進而刺激包括 GCSF，IL-6，IL-8，IL- 1b，CCL2 和 TNF-a。 Chow 等人於 2014 年進一步揭示了 NFkB 的激活是由乳腺癌衍生的外泌體和巨噬細胞之間的相互作用介導的，並且分別受巨噬細胞和腫瘤衍生的外泌體表面上 TLR2 和棕櫚酰化蛋白配體的存在的影響（37）。 在另一研究中，巨噬細胞中的 NFkB 通過將 miR-21 和 miR-29a（由腫瘤外泌體分泌）與鼠 TLR7 和人 TLR8 結合而激活，從而觸發 TLR 介導的促轉移性炎症反應，從而促進腫瘤的生長和轉移（39）。在乳腺癌衍生的外泌體中高表達的膜聯蛋白 A2，也在巨噬細胞介導的炎症反應中起作用（40）。 Annexin A2 通過增加 IL-6 和 TNF-a 的分泌來介導 M1 巨噬細胞活化。 用含有高 Annexin A 的乳腺癌衍生外泌體引發的動物導致肺和腦部 VEGFR1 水平升高，組織中 MMP9 相應升高。 腫瘤來源的外泌體上調 VEGFR1 和 MMP9 的表達分別與乳腺癌轉移，細胞外蛋白水解和血管生成有關（39）。

腫瘤外泌體對樹突狀細胞的促發炎作用

通過抑制樹突狀細胞分化，腫瘤來源的外泌體是有效的免疫抑制劑。 Yu 等人在 2007 年證明外泌體的施用引起小鼠脾臟中未分化的髓樣前體細胞的積累，並且體外將外泌體引入髓樣前體細胞導致分化的阻斷。樹突狀細胞分化的抑制作用是通過腫瘤來源的外泌體誘導 IL-6 介導的（41）。在黑色素瘤和結腸直腸癌中，腫瘤來源的外泌體能夠抑制人類單核細胞前體向樹突狀細胞的分化。這些單核細胞獲得了分泌 TGFb 的能力，從而進一步抑制了 T 淋巴細胞的增殖（42）。最近已經確定腫瘤衍生的外泌體（TEX）激活的樹突狀細胞（Ta-TEXs）能夠增加樹突狀細胞炎性介質的產生，包括 IL-6 和前列腺素 E1（PGE1）。在腫瘤來源的外泌體表面膜上發現的天然配體 Hsp105 與 TLR2 和 TLR4 的結合刺激了 IL-6 和 PGE1 的分泌。這進而通過 STAT3 的磷酸化導致腫瘤細胞侵襲和轉移的增加，進而通過與 MMP9 啟動子結合而促進基質金屬肽酶 9（MMP9）的轉錄（43）。此外胰腺癌衍生的外泌體通過轉移 miR-203 下調了樹突狀細胞中 TLR4 表達的表達。這導致 TNF-α 和 IL-12 的表達隨後降低（44）。

腫瘤外泌體對骨髓衍生抑制細胞（MDSC）的促發炎作用

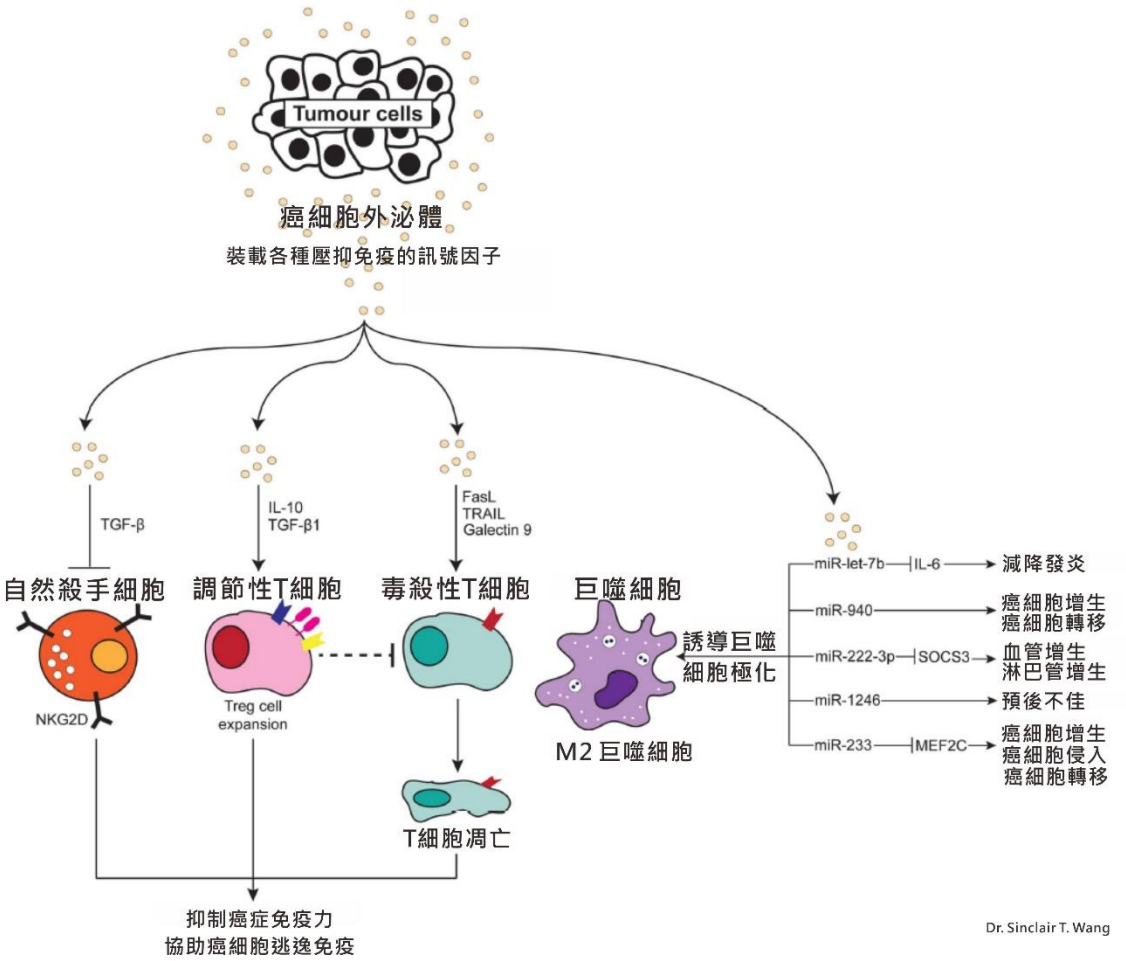
荷瘤小鼠（45）和人類（46, 47）中 MDSC 的積累，越來越多的證據表明腫瘤微環境產生了多種抑制這些免疫調節細胞成熟和分化的因子（48-50）。 通過抑制抗原加工和呈遞以及 T 細胞活化，MDSC 的積累已顯示在促進腫瘤進展中起作用，從而抑制了免疫監視和抗腫瘤免疫（51-53）。Yu 等人報導腫瘤來源的外泌體可被骨髓前體細胞吸收，並誘導這些髓樣細胞向 MDSC 途徑的分化途徑轉換（41）。腫瘤外泌體也被發現釋放促炎細胞因子 IL-6 和腫瘤生長因子 VEGF 進一步增強了其在腫瘤生長中的作用（56）。外泌體 Hsp70（57）和 Hsp72（56）均會擴展並誘導 MDSC 的激活。用外泌體 Hsp70 和 Hsp72 治療時，發現 MDSCs 顯著

增加促炎細胞因子（包括 IL-6，TNF-α，VEGF 和 CCL2）的產生，從而導致腫瘤生長和轉移的增加（56）。Liu 等人表明黑色素瘤外泌體對從 MyD88 基因敲除小鼠分離的骨髓（BM）前體細胞的分化沒有抑制作用，而從野生型小鼠分離的 BM 前體細胞則觀察到抑制作用。在暴露於黑色素瘤外泌體的野生型小鼠中，樹突狀細胞的百分比顯著降低，而在 MyD88 基因敲除小鼠中未觀察到顯著影響（57）。這表明 MyD88 在誘導 MDSC 中起著至關重要的作用。通過抑制巨噬細胞產生 IL-2，MDSCs 衍生的外泌體通過促進具有殺腫瘤表型的 M1 巨噬細胞向促進腫瘤的 M2 巨噬細胞的極化而促進腫瘤進展（58）。

腫瘤外泌體其他的促發炎作用

癌細胞與微環境之間的交流可以通過外泌體通過其載物的轉運來介導，這些載物包括蛋白質，DNA，信使 RNA 和微小 RNA（59, 61）。源自砷轉換的肝上皮細胞 L-02 細胞的外泌體可通過轉移外泌體 miR-155 在正常肝細胞中誘導促炎反應（62）。外泌體分泌蛋白質以會引發炎症反應，一項研究描述了從結直腸癌細胞衍生的外泌體釋放一種已知對蛋白質合成至關重要的酶賴氨酰-tRNA 合成酶（KRS），繼而誘導細胞因子和已知為 M1 和 M2 巨噬細胞標誌物的因子的釋放，包括 TNF-α，CXC 基序趨化因子配體 10（CRG2），IL-6 和 MMP9（63）。熱休克蛋白晶體蛋白 αB（CRYAB）會因暴露於促炎細胞因子 IL-1b 和 TNF-a 而從多形膠質母細胞瘤（GBM）衍生的外泌體釋放，從而發揮抗凋亡活性（64）。此外由於輻射或疾病，GBM 細胞中的細胞因子水平增加後，GBM 衍生的外泌體蛋白質組發生了顯著變化，這可能會促進炎症的進展，腫瘤的侵襲性，血管生成和腫瘤的進展（65） 。

腫瘤外泌體的抗發炎作用



腫瘤外泌體對免疫分子抗發炎作用的後果

腫瘤炎症的外泌體可通過引發免疫細胞凋亡來誘導免疫抑制（67），在愛潑斯坦-巴爾病毒（EBV）感染的鼻咽細胞中，釋放的外泌體含有高濃度的半乳凝素 9 蛋白，能夠誘導成熟的

Th1 淋巴細胞凋亡（67, 68），在大腸癌和黑色素瘤細胞中觸發活化的 CD8 + T 細胞依賴 Fas 依賴性凋亡的能力，從而有助於腫瘤從免疫系統逃逸（25，69，70）。

腫瘤外泌體對自然殺手細胞的抗發炎作用

腫瘤來源的外泌體抑制 NK 細胞的活性，作為促進癌細胞免疫逃逸的手段。這些腫瘤來源的外泌體能夠通過釋放免疫抑制性細胞因子轉化生長因子-b（TGF-b）來阻止 NK 細胞的發育（71）。在使用同系 BALB / c 和裸鼠的研究中，源自 TS / A 或 4T.1 鼠類乳腺腫瘤細胞的外泌體能夠通過抑制 IL-2 介導的 NK 細胞活化來誘導腫瘤生長（72）。NK 細胞的增殖也受到人乳腺和黑色素瘤細胞系產生的外泌體的抑制（72）。腫瘤來源的外泌體也已顯示出誘導 Smad 磷酸化，損害細胞毒性並降低 NKG2D 受體表達，這將導致腫瘤細胞表面標誌物的丟失（73-75）。外泌體能夠通過分泌 NKG2D 配體來充當誘餌，這會下調 NKG2D 受體介導的 NK 細胞的細胞毒性（76）。

腫瘤外泌體對調節性 T 細胞（Treg）的抗發炎作用

在癌症中發現 Treg 積累在腫瘤微環境中，並通過抑制各種免疫細胞，例如 T 淋巴細胞（77），B 淋巴細胞（78），NK 細胞（79），樹突狀細胞（80）和巨噬細胞（81）。與低密度 Treg 患者相比，腫瘤基質中高密度 Treg 患者的預後也較差（82）。腫瘤來源的外泌體可通過 Treg 的間接擴增和激活來啟動免疫抑制。這將導致 Treg 抑制功能的上調並增強 Treg 對細胞凋亡的抵抗力（83，84）。 Szajnik 等報導，與非癌性供體相比，骨髓瘤患者外周血中 CD24 + CD25 + FOXP3 + Treg 細胞的表達顯著增加，並且這些患者的血清中含有高濃度的腫瘤來源的外泌體。他們進一步確定，腫瘤來源的外泌體能夠通過涉及相關轉錄因子 IL-10 和 TGF-b1 磷酸化的機制誘導 Treg 擴增（84）。

腫瘤外泌體對巨噬細胞的抗發炎作用

在肝細胞癌中，外泌體能夠間接下調促炎性細胞因子 IL-6 的表達，作為抑制免疫系統的一種手段。一項研究表明 TLR4（85、86）被發現通過 MyD88 依賴性途徑通過釋放外泌體來調節不受控制的炎症。外泌體又將 miR-let-7b 轉移至巨噬細胞以抑制促炎性 IL-6 的表達，從而減弱了腫瘤的炎症（87）。在另一研究中發現巨噬細胞受到低氧卵巢癌細胞衍生的外泌體釋放的 miR-940 的過度表達的影響，從而誘導巨噬細胞的抗炎 M2 極化，從而促進上皮性卵巢癌（EOC）細胞的增殖和遷移（88）。另一富含 EOC 來源的外泌體的 miRNA miR-222-3p 也被發現增加了 M2 巨噬細胞的極化，從而促進了腫瘤微環境中的血管生成和淋巴管生成，從而進一步促進了 EOC 的發展（89）。miR-222-3p 直接靶向 SOCS3（細胞因子信號傳導抑制劑 3），它是 JAK / STAT 通路的負調節劑（92），已被描述為控制 M1 和 M2 巨噬細胞的極化（91-93）。 研究發現 SOCS3 表達的抑制與 STAT3 激活的表達增加相關（94）。

在暴露於具有功能獲得性突變體 p53 的結腸癌細胞釋放的外泌體的巨噬細胞中，也可以看到向 M2 極化的轉變。 這些外泌體含有顯著高水平的 miR-1246，當轉移至鄰近的巨噬細胞時，它會刺激抗炎細胞因子和上皮間充質（EMT）促進因子的分泌增加，從而導致腫瘤形成和預後不良（95）。 外泌體介導 M2 巨噬細胞極化的另一種方法是遍歷單核細胞的細胞質，以誘導肌動蛋白細胞骨架的形態變化和重組。 這些膠質母細胞瘤衍生幹細胞（GSC）分泌的外泌體通過與 STAT3 結合刺激單核細胞程序性死亡配體 1（PD-L1）的增加，從而介導這種抑制性開關（94）。反過來，巨噬細胞也能夠誘導外泌體的釋放，以將 miRNA 穿梭到微環境中的相鄰細胞中。 響應抗炎分子 IL-4 的激活，來自乳腺癌腫瘤的巨噬細胞已顯示出釋放含 miR-233 的外泌體的能力，該 miR-233 通過直接靶向肌細胞增強因子（Mef2c）在腫瘤的生長，侵襲和轉移中起作用（96）。

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